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Title page

Inter-observer variation in delineating the coronary arteries as organs at risk

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Abstract

Purpose

To determine the inter-observer variation in delineating the coronary arteries as organs at risk (OARs) in breast cancer (BC) radiotherapy (RT) and how this variation affects the estimated coronary artery radiation dose.

Method

Delineation of the left main and the left anterior descending coronary artery (LMCA and LAD), and the right coronary artery (RCA), by using the heart atlas by Feng et al, was performed by three radiation oncologists in 32 women who had received adjuvant RT for BC. Centres of the arteries were calculated and distances between artery centres were measured and the artery radiation doses were estimated. The intraclass correlation coefficient (ICC) was used to quantify the variability in doses.

Results

Along the extent of RCA, the median distance between centres of arteries varied from 2 to 9 mm with similar patterns over pairs of oncologists. For the LMCA-LAD the median distance varied from 1 to 4 mm. The estimated maximum radiation doses showed an ICC variation from 0.82 to 0.97.

Conclusion

The coronary arteries can be reliably identified and delineated as OARs in BC RT. The spatial variance is limited and the total variation in radiation dose is almost completely determined by the between patient variation.

Introduction

Breast cancer (BC) is the most common cancer form and cause of cancer death in women [1]. Adjuvant radiotherapy (RT) is standard treatment after breast conserving surgery (BCS) and in the case of lymph node metastases [2]. Large meta-analysis show significant benefits in terms of reducing local recurrences and breast cancer deaths [3, 4]. In node-negative, and node-positive disease, respectively, an absolute 5-year risk reduction of 16.1%, and 30.1% for local recurrences, and an absolute risk reduction in 15-year-breast cancer mortality of 5.1%, and 7.1% were shown, when RT was given after BCS. In patients undergoing mastectomy and axillary clearance and with lymph node metastasis, an absolute 5-year risk reduction of 17.1% for local recurrence, and 5.4% for 15-year breast cancer mortality, was shown after RT to the chest wall and regional lymph nodes [3, 4].

RT on the other hand increases the risk for heart disease due to incidental irradiation of the heart [5]. Trials have shown an increase in cardiac mortality and morbidity, and a relationship between higher absorbed radiation dose and a higher incidence of ischemic heart disease (IHD) [5-7]. In some studies, RT to the left breast is associated with higher risk of IHD than RT to the right breast, probably due to the localization of the heart [8, 9]. Dosimetry studies have shown that the left anterior descending artery (LAD) receives

the highest radiation doses [10, 11] and a higher incidence of coronary artery stenosis in the LAD has also been shown after RT of left-sided BC [12, 13].

The relationship between absorbed radiation dose to the coronary arteries and IHD has raised the question whether coronary arteries should be regarded as separate organs at risk (OAR) in RT. Historically the heart has been regarded as an OAR. The radiation tolerance for the coronary arteries may however be different from other cardiac structures, and there are no current models for normal tissue complication probability (NTCP) concerning coronary artery toxicity [14]. The radiation volumes and doses to the heart have changed during the last decades due to the development of new radiation techniques but radiation doses to the most anterior part of the heart may still be high [11, 15].

A better understanding of radiation tolerance of the coronary arteries is important in order to form recommendations concerning dose constraints and consistent clinical guidelines. Modern three-dimensional (3 D) RT is based on the delineation of target volumes and OARs in the computerised tomography (CT) scan. Consistency in delineation is crucial in further development of NTCP models for coronary arteries and in the clinical practice to optimize the RT plan for each patient. Several studies have documented significant inter-observer variation in delineation of target volumes and OARs [16-18]. One previously published study on reproducibility of delineating coronary arteries showed a substantial inter-observer variation in estimated dose [19]. The aim of the present study was to determine the degree of inter-observer variation in delineating the coronary arteries as OARs, and to assess the relationship between inter-

observer and inter-patient variability in estimated radiation doses to the coronary arteries.

Patients and methods

Patients

The patients were defined from a larger cohort of irradiated women with BC who subsequently developed coronary artery stenosis requiring percutaneous coronary intervention. To identify the cohort, we selected women diagnosed with BC in three health care cancer regions of Sweden (Uppsala-Örebro, Stockholm and the Northern region) during the period 1992-2012 who had received adjuvant RT according to the Breast Cancer Quality of Care registers. This BC cohort was then linked to the Swedish Coronary Angiography and Angioplasty Register, a part of the nationwide Swedish cardiac register SWEDEHEART [20]. For the present study all women treated at one of the radiotherapy departments, the Department of Oncology at the hospital of Gävle, were selected. Information concerning BC surgery, adjuvant endocrine therapy, chemotherapy, and tumour characteristics (invasive cancer or cancer in situ, size, grade, and nodal status) were obtained from the Breast cancer quality of care registers.

Information regarding radiation targets, fractionation, total radiation dose, and CT slice thickness was retrieved from the radiotherapy charts. For dose estimation, the dose distribution from the treatment plans was used and all dose estimation was done in the

Eclipse® treatment planning system (Varian Medical Systems Inc., Palo Alto, California USA) using the analytical anisotropic algorithm (AAA). Patients treated from 1997 to 2005 were planned with the older system TMS® (Helax AB, Uppsala, Sweden) and for study purpose their treatment plans and CT scans were imported to the Eclipse system for delineation and dose calculation. The ethical committee (EPN) of Northern Sweden approved the study.

Delineation

The contouring of the coronary arteries was performed in the Eclipse dose planning system by three clinically experienced radiation oncologists from different centres in Sweden, independently of each other. The validated heart atlas by Feng et al was used as a guideline for the delineation of the coronary arteries and delineation was attempted in each CT slice [21]. The left main coronary artery (LMCA), the left anterior descending artery (LAD), and the right coronary artery (RCA) were delineated and the arteries were divided into segments corresponding to the proximal, mid, and distal parts of the arteries (Figure 1). In the majority of the CT slices, the coronary arteries were visible but in difficult cases anatomical landmarks such as the left interventricular, left atrioventricular, and the right atrioventricular grooves were followed and the interpolation function in the target planning system was used. No extra margin was added to the contours.

Evaluation of inter-observer variation in spatial distance

In order to evaluate the spatial variation, the x-, y-, and z-coordinates of the centre of the arteries LMCA-LAD and RCA were determined for each of the 96 combinations of the 32 patients and the three radiation oncologists. The CT-slices determined the z-coordinate, whereas the x- and y-coordinates were determined using the centres of mass of the contoured area. For the sections of the arteries running in the same plane as the CT slices, the artery centre point was determined as a weighted average of the centres of mass of the contoured areas. The weights were proportional to the contour areas. By applying this procedure sequences of *n* coordinates $\{(x_1, y_1, z_1), (x_2, y_2, z_2),\ldots,(x_n, y_n, z_n)\}$, were retrieved, one sequence for LMCA-LAD and one for RCA for each combination of woman and contouring radiation oncologist. The size of *n* will vary depending on artery, woman, the number of CT slices, and contouring radiation oncologist. Each sequence of points were joined by a straight line to form a three dimensional curve representing the midpoint of the artery. This is illustrated in figure 2 a, showing a CT-scan of a representative patient, in which the three different contouring radiation oncologists LMCA-LAD and RCA-curves are plotted.

To measure the spatial difference in mm between the different curves, a three-step procedure was applied to each of the studied patients. At first the start- and end-points of the curves were determined (Figure 2 b). The choice of start point (one point for each of the three curves) was determined by comparing the results from three potential alternatives. Firstly, the point selected by oncologist A was used, denoted $start_A$, and the

distance to the points on the curves B and C with the shortest distance to $start_A$, measured. For oncologist B and C similarly the closest points between the start points, $start_B$ and $start_C$, were measured respectively, and the curves depicted by the two others. The final choice was the one that minimized the distance between the three points. The ending points were selected in a similar manner. Finally, the six curves were subdivided into 1001 equidistant points. The distance between these points were determined for each pair of radiation oncologists. The variation in distances between the 32 patients was displayed by calculating the median, 25th and 75th percentiles.

Evaluation of inter/intra-study subjects dose estimates

LMCA-LAD and RCA were split in three parts (proximal, mid, and distal), according to Figure 1, which represents a schematic overview of the heart and the distribution of the coronary arteries. For each of the seven parts of the arteries (also referred to as segments) the variance in estimated doses was calculated, depending of the variance between radiation oncologists, the variance within study subjects, and the variance between the 32 study subjects. The intraclass correlation coefficient (ICC) was derived as a measurement of agreement between observers. A value of ICC=1.0 would indicate that the difference between the doses only would be due to the inter-patient variation and a value of ICC=0 would indicate that the difference would only be due to variation between the contouring radiation oncologists. The results are presented based on mean and maximum doses. A subgroup consisting of 22 study subjects with CT slice thickness of 5 mm or less is presented separately.

Results

A total of 52 women who had received RT at the Department of Oncology of Gävle hospital, according to the Breast Cancer Quality of Care register, were identified in the main study cohort and this sub-cohort was used in the present study. Twenty out of 52 women were further excluded, nine did not have a 3-D CT-based RT planning, six had missing RT plans, and finally five did not receive RT. The final cohort thus consisted of 32 women who had received adjuvant RT due to breast cancer from 1997 to 2012. The patient characteristics are shown in Table 1. The age at diagnosis varied from 40 to 83 years and the majority of the patients had screening detected, invasive cancers with a tumour size less than 20 mm, without lymph node metastases. The majority were treated with BCS and RT to the breast. Out of these, 31 patients were treated with a fractionation of 2 Gy x 25, and one with a fractionation of 2.67 Gy x 16.

The CT scans had a slice thickness varying from 2 to 15 mm. Twenty-two of the patients had CT slices of 5 mm or less, nine had CT slices of 10 mm, and one of 15 mm. The distance in mm between the centres of the delineated arteries in each CT slice following the arteries from the origin at the root of the aorta to the most distal segment is shown in Figure 3. The Result for the 22 patients with CT slices of 5 mm or less is presented in Figure 3, since CT slices of 5 mm or less can be considered as more applicable to modern RT techniques. The three different combinations, i.e: radiation oncologists A vs. B, A vs. C, and B vs. C, are shown for RCA and LMCA-LAD, respectively. For the RCA, the median distance between the centre points varies from 2 to 9 mm and the greatest differences were seen in the mid and distal parts of the artery. For the LMCA-LAD, the median distance varies from 1 to 4 mm with the greatest differences in the mid and distal LAD.

The results were similar when patients with CT slices from 10-15 mm were included (data not shown).

The variation of estimated mean and maximum doses to the arteries is shown in Table 2. The estimated radiation doses in right-sided and left -sided BC are shown separately due to the large differences in dose between right-sided and left-sided BC in some parts of the arteries. The doses in RCA were low with mean doses varying from 0.2 to 4.3 Gy, and maximum doses varying from 0.2 to 9.1 Gy, with the highest doses seen in the mid RCA of right-sided BC. In the LMCA-LAD the mean dose varied from 0.0-50.4 Gy, and the maximum dose varied from 0.1 to 51.3 Gy. The highest doses were seen in the mid and distal LAD of left sided BC. The ICC varied from 0.73 to 0.99 indicating that most of the variation in estimated doses can be explained by differences between study subjects rather than the contouring radiation oncologists. The ICC is presented for the whole cohort and for the patients with CT slice thickness of 5 mm or less separately.

Discussion

In the present study of inter-observer variation in delineating the coronary arteries under conditions similar to the clinical routine, a good spatial agreement between three radiation oncologists was found, especially for the high-dose region of LAD. The median distance between the centres of the delineated arteries was 1-4 mm for LMCA-LAD. The same consistency was not shown for the RCA, in which the distance between the centres varied from 2 to 9 mm. The estimated maximum doses to the RCA were in general low with max doses varying from 0.2-9.1 Gy with the highest doses seen in right-sided RT. In the LAD the estimated doses were uniformly high in mid and distal parts of the LAD in

left-sided RT with maximum doses corresponding to the doses of the breast target of approximately 50 Gy.

These results show that delineation of LMCA-LAD can be performed with an acceptable concordance between radiation oncologists, and that the high estimated doses seen in the mid and distal parts of the artery clearly show an urgent need of classifying of LMCA-LAD as an OAR in left-sided RT. If the internal mammary chain will be included in the radiation field more frequently and if modern radiotherapy techniques like intensity-modulated radiation therapy will be used in a wider extent, this might also influence the absorbed dose to the RCA and make delineating of this artery important as well.

The evaluation of the estimated doses showed an ICC varying from 0.76 to 0.98 for LMCA-LAD and clearly demonstrates the reliability of delineating this artery between radiation oncologists. The high ICC indicate that in order to increase the power of in future dose response studies of cardiac side effects from RT, effort should be put on including more patients to the study rather than using several contouring radiation oncologists. For the RCA the ICC were slightly lower and varied from 0.73 to 0.92, suggesting that it might be of value to use several contouring radiation oncologists to allow for statistical methods taking measurement errors into account.

The patients that were included in the study were treated from 1997 to 2012, and the CT scan series from the early treatments were performed with a slice thickness up to 15 mm, which can be considered as a weakness. However, analysis of patients with CT scans with slices of 5 mm or less, showed an ICC similar when compared to the whole cohort. The consistency for the delineation of LMCA-LAD would likely be even better if

all patients had been planned using CT series with a currently used slice thickness of 2 mm. All the included patients were treated in the same department and this may be considered as a limitation of the study, since RT techniques may vary between institutions.

Several studies have shown that high absorbed dose to the coronary arteries increases the risk of developing coronary stenosis leading, to IHD events as angina pectoris and myocardial infarction [5, 12, 13]. However, in a recent large population based study from Scandinavia, a statistical model including doses to the LAD in addition to the whole heart, failed to improve the association between radiation doses and the risk of coronary events [6]. In order to estimate and limit the dose to the coronary arteries, they need to be defined and delineated in RT planning. The previous studies concerning inter-observer variation in delineation of the coronary arteries have focused on LAD and have shown a substantial variation in delineation and estimated dose to the artery [19, 22]. This has raised a question concerning the reliability of dose reporting in retrospective studies, and how estimated doses to LAD should be handled in clinical practice.

In a study by Vennarini et al, only a third of the LAD was visible and the distal parts of LAD were the most difficult to visualize [22]. In a Danish study by Lorenzen et al, the inter-observer variation in delineating the LAD with or without guidelines was studied [19]. The guidelines used in that study were the validated CT atlas by Feng [21]. The study reported a reduced inter-observer variation concerning the length of the LAD but an increased variation in the left-right (L-R) and anterior-posterior (A-P) plane when the guidelines where used [19]. The estimated doses varied substantially and the consistency was not improved by using guidelines [19]. The design of the present study

differed from the Danish study but the same CT atlas by Feng et al was used [19, 21]. The spatial variation in delineating the LAD was lower in the present study in comparison to the Danish study [19]. In contrast to the studies by Lorenzen and Vennarini and al [19, 21], a decrease in consistency in the most distal parts of the LAD was not observed in the present study.

Sufficient margins to cover the uncertainties of the delineation and the motion of the heart and respiration have to be taken in to account. White et al have studied the impact of cardiac and respiratory movement on the accuracy of LAD delineation [23]. The conclusion of their study was that a margin of 2 mm in the A-P and L-R plane and of 4 mm in the inferior-superior plane should be added on the contour delineated by the physician [23]. In a study by Dodge et al, using arteriograms, the diameter of LAD is estimated to 3,7±0,4 mm in the proximal and to 1,9±0,4 mm in the distal parts [24]. In terms of cardiac and respiratory motion, a diameter of 6 mm when delineating the LAD should be considered as sufficient based on the results of the present study and the study by White et al [23]. The use of intravenous contrast may further improve the accuracy of contouring the coronary arteries.

The present study shows that it is feasible to delineate the LMCA-LAD in RT planning with acceptable inter-observer spatial variation and this is proposed to become clinical practice.

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Table 1. Patient characteristics by laterality of breast cancer.

	Right-sided BC (n=13)		Left-sided BC (n=19)		All BC (n=32)	
Year of breast cancer diagnosis, n (%)						
1997-2001	6	(46)	4	(21)	10	(31)
2002-2007	4	(31)	7	(37)	11	(34)
2008-2012	3	(23)	8	(42)	11	(34)
Age at breast cancer diagnosis, n (%)						
40-49 yrs	2	(15)	2	(10)	4	(13)
50-59 yrs	4	(31)	2	(10)	6	(19)
60-69 yrs	6	(46)	6	(32)	12	(37)
70-79 yrs	1	(8)	6	(32)	7	(22)
80-83 yrs	0	(0)	3	(16)	3	(9)
Mode of detection, n (%)						
Clinically detected	1	(8)	7	(37)	8	(25)
Screening detected	12	(92)	12	(63)	24	(75)
Cancer type, n (%)						
In situ	1	(8)	2	(10)	3	(9)
Invasive	12	(92)	17	(90)	29	(91)
Tumour size, n (%)						
≤20 mm	13	(100.0)	13	(68)	26	(81)
21-50 mm	0	(0)	4	(21)	4	(13)
>50 mm	0	(0)	2	(11)	2	(6)
N-stage, n (%)						
N0	8	(62)	15	(79)	23	(72)
N+	2	(15)	1	(5)	3	(9)
NX/Missing	3	(23)	3	(15)	6	(19)
Grade, n (%)						
1	4	(31)	2	(11)	6	(19)
2	7	(54)	12	(63)	19	(59)
3	0	(0)	3	(16)	3	(9)
Missing	2	(15)	2	(11)	4	(13)
Type of surgery, n (%)						
BCS	13	(100.0)	14	(74)	27	(84)
Mastectomy	0	(0)	5	(26)	5	(16)
Endocrine therapy, n (%)						
Endocrine therapy	2	(15)	12	(63)	14	(44)
No endocrine therapy	11	(85)	7	(37)	18	(56)

Chemotherapy, n (%)						
Chemotherapy	1	(8)	4	(21)	5	(16)
No Chemotherapy	12	(92)	15	(79)	27	(84)
CT-scan slice thickness, n (%)						
2 mm	1	(8)	3	(16)	4	(13)
2.5 mm	3	(23)	6	(32)	9	(28)
5 mm	3	(23)	6	(32)	9	(28)
10 mm	5	(38)	4	(21)	9	(28)
15 mm	1	(8)	0	(0)	1	(3)
Target, n (%)						
Breast	12	(92)	12	(63)	24	(75)
Breast + reg LN	1	(8)	1	(5)	2	(6)
Breast + reg LN + IMC	0	(0)	1	(5)	1	(3)
Chest wall + reg LN	0	(0)	4	(21)	4	(13)
Chest wall + reg LN + IMC	0	(0)	1	(5)	1	(3)
Fractionation, n (%)						
2 Gy x 25	9	(69)	19	(100)	28	(88)
2 Gy x 27	2	(15)	0	(0)	2	(6)
2.67 Gy x 15	1	(8)	0	(0)	1	(3)
2 Gy x 25 + boost 2 Gy x 8	1	(8)	0	(0)	1	(3)

Breast cancer (BC), years (yrs), breast conserving surgery (BCS), regional lymph nodes i.e; axillar and supraclavicular lymph nodes (reg LN), internal mammary chain (IMC), Gray (Gy).

Table 2. Range of minimum, median and maximum of mean and maximum radiation dose in Gray by laterality of breast cancer (BC) for the segments of the coronary arteries, with intraclass correlation coefficient (ICC) for the three different radiation oncologists: A, B, and C. The ICC for a subgroup consisting of patients with CT slice thickness of 5 mm or less is presented separately. The right coronary artery (RCA), the left main coronary artery (LMCA) and the left anterior descending artery (LAD) are shown.

Mean doses	**Minimum of mean dose**	**Median of mean dose**	**Maximum of mean dose**		**All patients**	**Restricted to patients with CT-slices of max 5 mm**	
	Range for 3 radiation oncologists	Range for 3 radiation oncologists	Range for 3 radiation oncologists	**ICC**	**ICC** (Left/right combined)	**ICC**	**ICC** (Left/right combined)
Proximal RCA							
Right-sided BC	0.4 - 0.5	0.9 - 1.0	1.7 - 1.8	0.87	0.91	0.86	0.91
Left-sided BC	0.5 - 0.8	1.2 - 1.4	2.5 - 2.6	0.92		0.92	
Mid RCA							
Right-sided BC	0.9 - 1.0	1.4 - 1.5	4.0 - 4.3	0.83	0.88	0.83	0.88
Left-sided BC	0.2 - 0.3	0.8 - 0.9	1.7 - 2.0	0.86		0.86	
Distal RCA							
Right-sided BC	0.3 - 0.4	0.7 - 1.0	1.6 - 1.8	0.73	0.77	0.74	0.78
Left-sided BC	0.2 - 0.3	0.6 - 0.6	1.4 - 1.7	0.78		0.78	
LMCA							
Right-sided BC	0.2 - 0.3	0.5 - 0.5	0.7 - 0.9	0.84	0.92	0.84	0.92
Left-sided BC	0.7 - 0.7	1.0 - 1.3	1.9 - 2.3	0.83		0.83	
Proximal LAD							
Right-sided BC	0.1 - 0.2	0.3 - 0.3	0.5 - 0.5	0.88	0.94	0.88	0.94
Left-sided BC	0.9 - 1.2	1.7 - 2.0	8.7 - 13.1	0.92		0.92	
Mid LAD							
Right-sided BC	0.0 - 0.1	0.1 - 0.1	0.3 - 0.4	0.97	0.84	0.97	0.84
Left-sided BC	2.3 - 2.5	5.3 - 7.2	29.2 - 33.0	0.76		0.76	
Distal LAD							
Right-sided BC	0.0 - 0.0	0.0 - 0.1	0.3 - 0.3	0.98	0.99	0.98	0.99
Left-sided BC	7.0 - 10.9	39.5 - 43.6	49.7 - 50.4	0.96		0.96	

Maximum	**Minimum**	**Median of**	**Maximum**		**All patients**	**Restricted to**

doses	of maximum dose	maximum dose	of maximum dose			patients with CT-slices of max 5 mm	
	Range for 3 radiation oncologists	Range for 3 radiation oncologists	Range for 3 radiation oncologists	**ICC**	**ICC** (Left/right combined)	**ICC**	**ICC** (Left/right combined)
Proximal RCA							
Right-sided BC	0.6 - 0.9	1.3 - 1.6	2.4 - 2.7	0.75	0.84	0.75	0.84
Left-sided BC	0.8 - 1.0	1.6 - 1.6	2.7 - 3.0	0.90		0.90	
Mid RCA							
Right-sided BC	1.3 - 1.5	2.1 - 2.3	5.5 - 9.1	0.61	0.75	0.61	0.75
Left-sided BC	0.2 - 0.5	1.2 - 1.3	2.6 - 3.1	0.84		0.84	
Distal RCA							
Right-sided BC	0.5 - 0.8	1.2 - 1.8	2.8 - 3.3	0.80	0.83	0.80	0.83
Left-sided BC	0.4 - 0.4	0.7 - 0.8	1.8 - 2.3	0.78		0.78	
LMCA							
Right-sided BC	0.2 - 0.4	0.6 - 0.6	1.0 - 1.1	0.88	0.91	0.88	0.90
Left-sided BC	0.8 - 0.8	1.3 - 1.6	2.5 - 3.5	0.82		0.82	
Proximal LAD							
Right-sided BC	0.2 - 0.3	0.4 - 0.4	0.6 - 0.7	0.86	0.98	0.85	0.98
Left-sided BC	1.1 - 1.8	2.2 - 2.8	22.1 - 24.6	0.97		0.97	
Mid LAD							
Right-sided BC	0.0 - 0.1	0.2 - 0.2	0.4 - 0.5	0.89	0.92	0.88	0.91
Left-sided BC	3.6 - 4.8	16.6 - 35.7	45.4 - 48.5	0.84		0.84	
Distal LAD							
Right-sided BC	0.0 - 0.0	0.1 - 0.1	0.4 - 0.5	0.97	1.00	0.97	0.99
Left-sided BC	16.7 - 33.6	47.1 - 47.5	51.0 - 51.3	0.85		0.85	

Figure 1
The coronary arteries: the right coronary artery (RCA), the left main coronary artery (LMCA), the left anterior descending artery (LAD), and the left circumflex artery (LCX). RCA and LAD further subdivide into three segments: Proximal, Mid, and Distal.

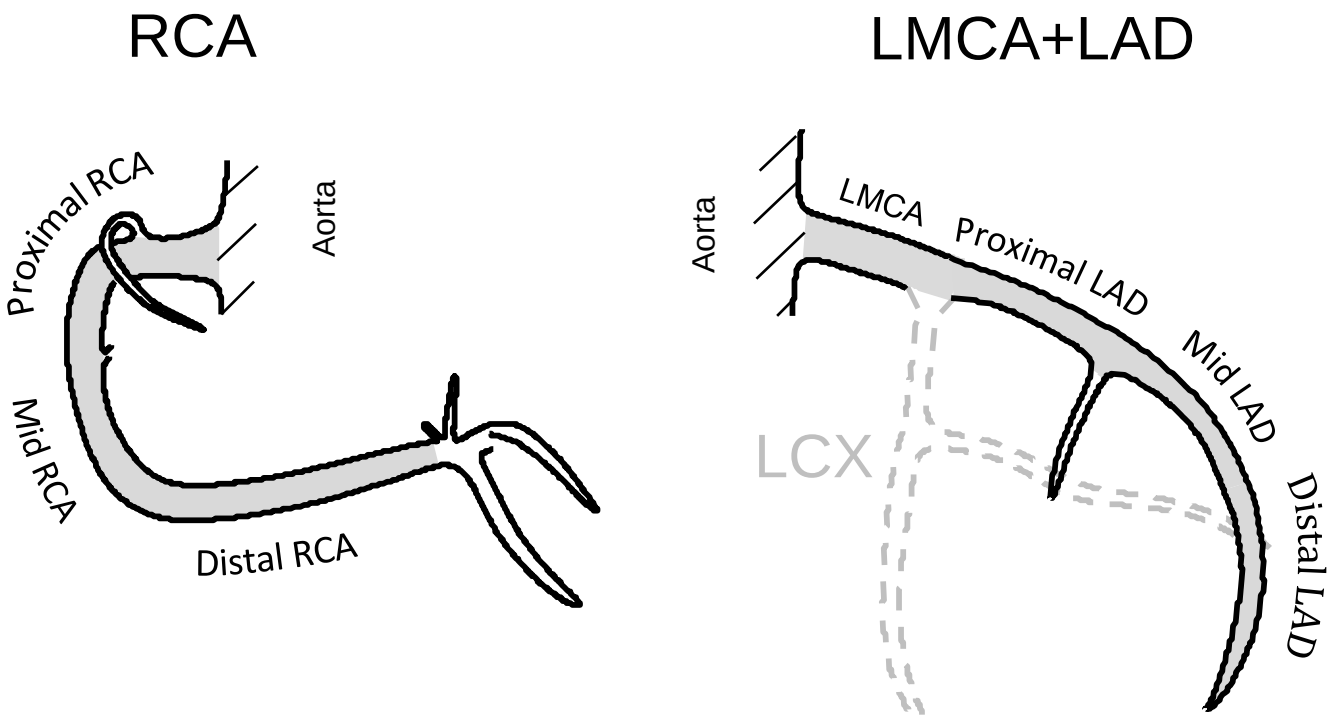
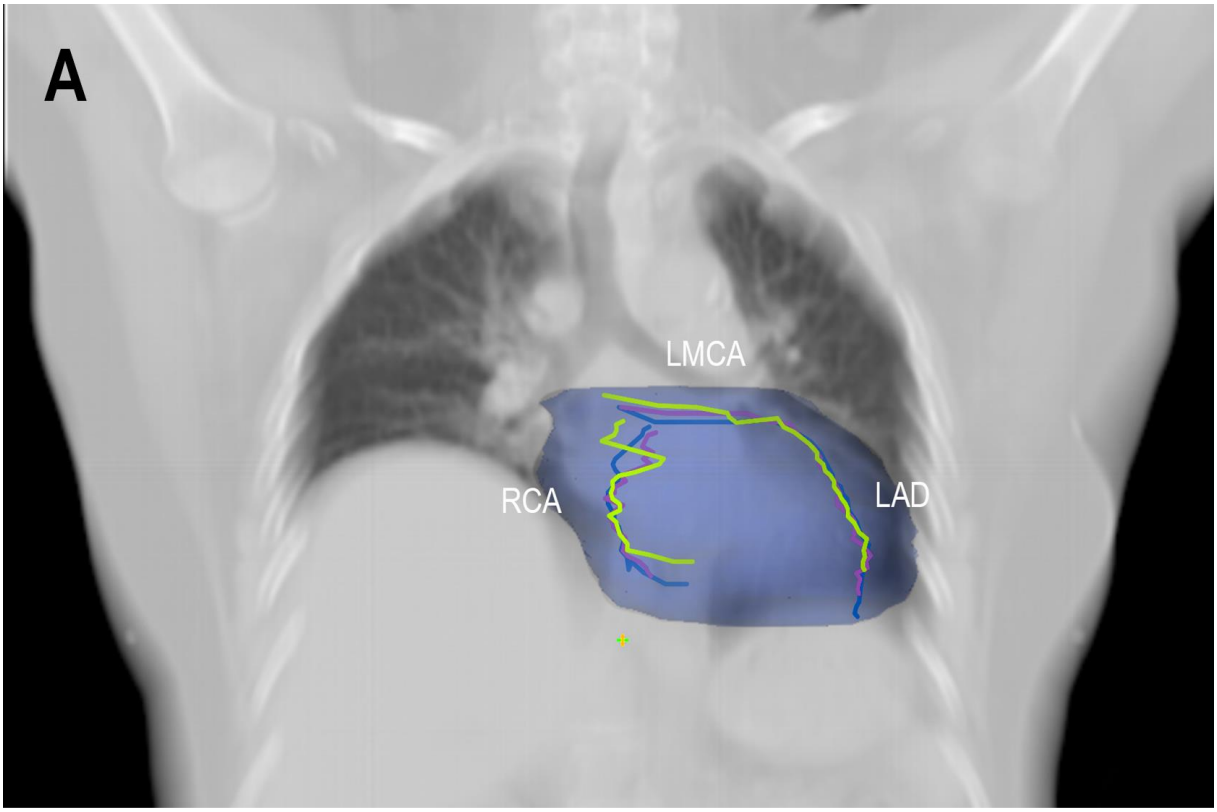


Figure 2

Figure 2 a: CT-scan of a representative patient, in which the three different radiation oncologists LMCA-LAD and RCA-curves are plotted.

Figure 2 b: The definition of the start and end points of the curves.



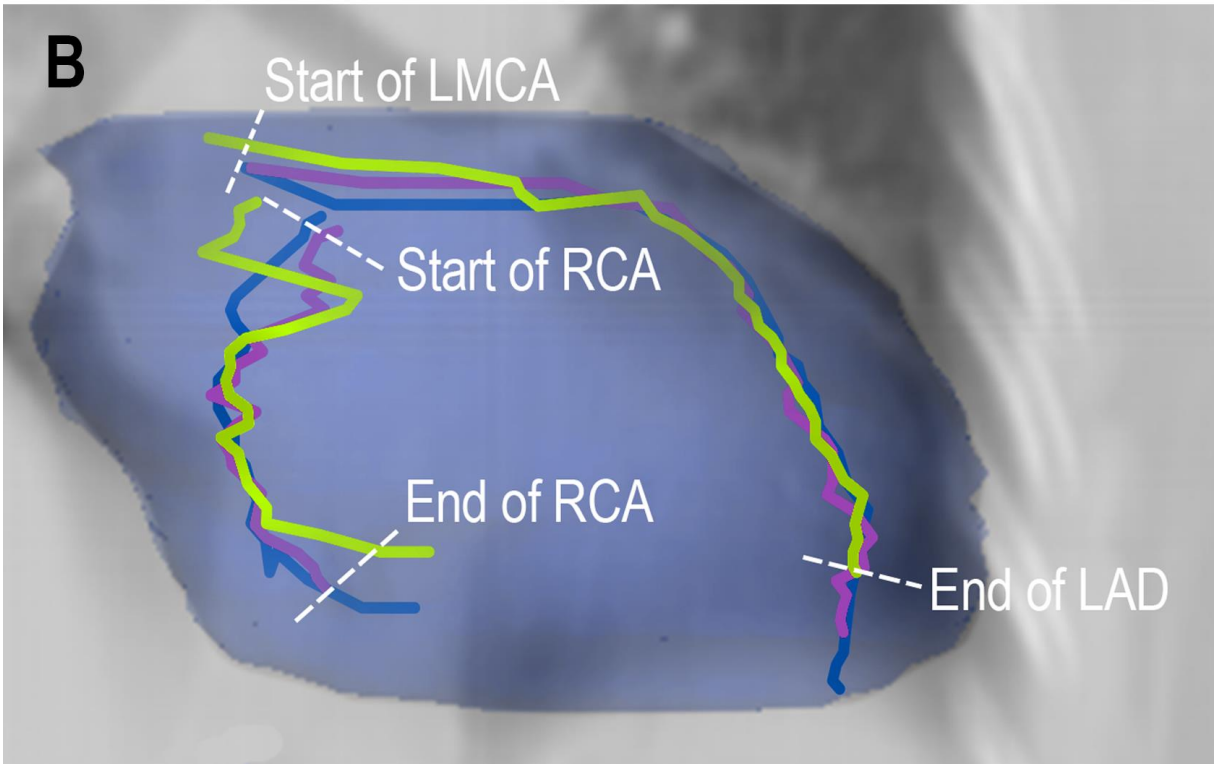


Figure 3

The variation in distances between the centres of the arteries delineated by the three radiation oncologists for the 22 women with CT slice thickness of 5 mm or less. The 25th percentile, the median and the 75th percentile are shown. Breast cancer (BC), right coronary artery (RCA), LMCA (left main coronary artery), LAD (left ascending coronary artery).